

Clostridium septicum Infection and Malignancy

MARK R. KATLIC, M.D., WAYNE M. DERKAC, M.D., WILLIAM S. COLEMAN, M.D.

*From the General Surgical Services,
Massachusetts General Hospital,
Boston, Massachusetts*

Evidence mounts favoring the relationship, albeit unexplained, between *Clostridium septicum* infection and malignancy, particularly hematologic or intestinal malignancy. Seven patients with *C. septicum* gangrene or sepsis have been treated at the Massachusetts General Hospital in the years 1977–79. All of these patients have had associated malignant disease: four patients had colon adenocarcinomas, two patients had acute myeloblastic leukemias, and one patient had breast carcinoma. In six of the seven patients, the malignancy was in an advanced state; the breast carcinoma showed no evidence of recurrence after mastectomy, 17 years earlier. A bowel portal of entry is postulated in five patients. Despite prompt use of appropriate antibiotics, the only survivors were two of the four patients, who underwent early extensive debridement. These results suggest that, in the patient with *C. septicum* infection, malignancy should be sought; that, in the septic patient with known malignancy, *C. septicum* should be considered; and that, in the absence of external source in the patient with clostridial myonecrosis or sepsis, the cecum or distal ileum should be considered a likely site of infection. Increased awareness of this association between *C. septicum* and malignancy, and aggressive surgical treatment, may result in improvement in the present 50–70% mortality rate.

CIVILIAN INFECTION WITH *Clostridium septicum* was once thought to be exceedingly rare; in a review of the world literature, 1940–1967, Alpern and Dowell¹ found only 11 such cases. Subsequently, they presented 27 patients for the period 1963–1968, and a recent report from their center discusses a 1969–1977 series of 59 cases.² Improved anaerobic laboratory techniques appear to be responsible, in great part, for the increased awareness of this organism's pathogenetic potential.

The authors of several series, moreover, have suggested a relationship between *C. septicum* infection and malignancy, especially hematologic or colonic malignancy. Of Alpern and Dowell's¹ 27 patients, 23 (85%) had malignancy; 14 of the malignancies were leukemia and 6 malignancies were colon carcinoma. Four of five patients with *C. septicum*, in a 1976 British report,³ had large bowel cancer, and in the series of Koransky et al.,² 42 (71%) of 59 patients had malig-

nancies; 16 of these were leukemia, 5 malignancies were lymphomas or sarcomas, 14 malignancies colon cancers, and there were seven other solid malignancies. A further series⁴ of patients with nontraumatic myonecrosis (not documented as due to *C. septicum*) showed six of ten patients had colon adenocarcinoma and two others had leukemia.

The striking clinical course of our first patient (case 1), a man with *C. septicum* gas gangrene and unsuspected leukemia, prompted us to review the Massachusetts General Hospital experience with *C. septicum* infection, and to evaluate the role of surgery in treating this pernicious disease. This series comprises all cases of *C. septicum* gangrene or sepsis treated at the Massachusetts General Hospital in the period January 1, 1977 through December 31, 1979. Seven patients were treated, five men and two women. The mean age of the patients was 55 years (range: 29–71 years). All the patients were Caucasians living in New England.

Case Reports

Case 1. A 50-year-old man, with a past history of mild esophagitis and allergy to penicillin, walked into the emergency room complaining of abdominal and left thigh pain of eight hours duration. On examination, the patient's abdomen was distended and tender, and his left thigh was tensely swollen and ecchymotic; his temperature was 40 C and his pulse was 140. A radiograph of the patient's thigh showed extensive gas in the soft tissues, and an aspiration specimen of brownish fluid from the thigh had many gram positive rods (Fig. 1). A differential white blood cell count and subsequent bone marrow aspiration specimen indicated a previously undiagnosed acute myeloblastic leukemia. Radical surgery was dismissed by the patient and his family; antibiotic therapy was initiated. The patient's thigh became tense, crepitant, and discolored from the lower abdomen to the knee, and ten hours after admission he died. Autopsy examination demonstrated left thigh gas gangrene, acute myeloblastic leukemia, and hemorrhagic necrosis of the terminal ileum and ascending colon without leukemic involvement. Thigh aspiration specimens and blood cultures grew *C. septicum*.

Case 2. A 29-year-old man, with a history of acute myeloblastic

Reprint requests: Mark R. Katlic, M.D., Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts 02114.

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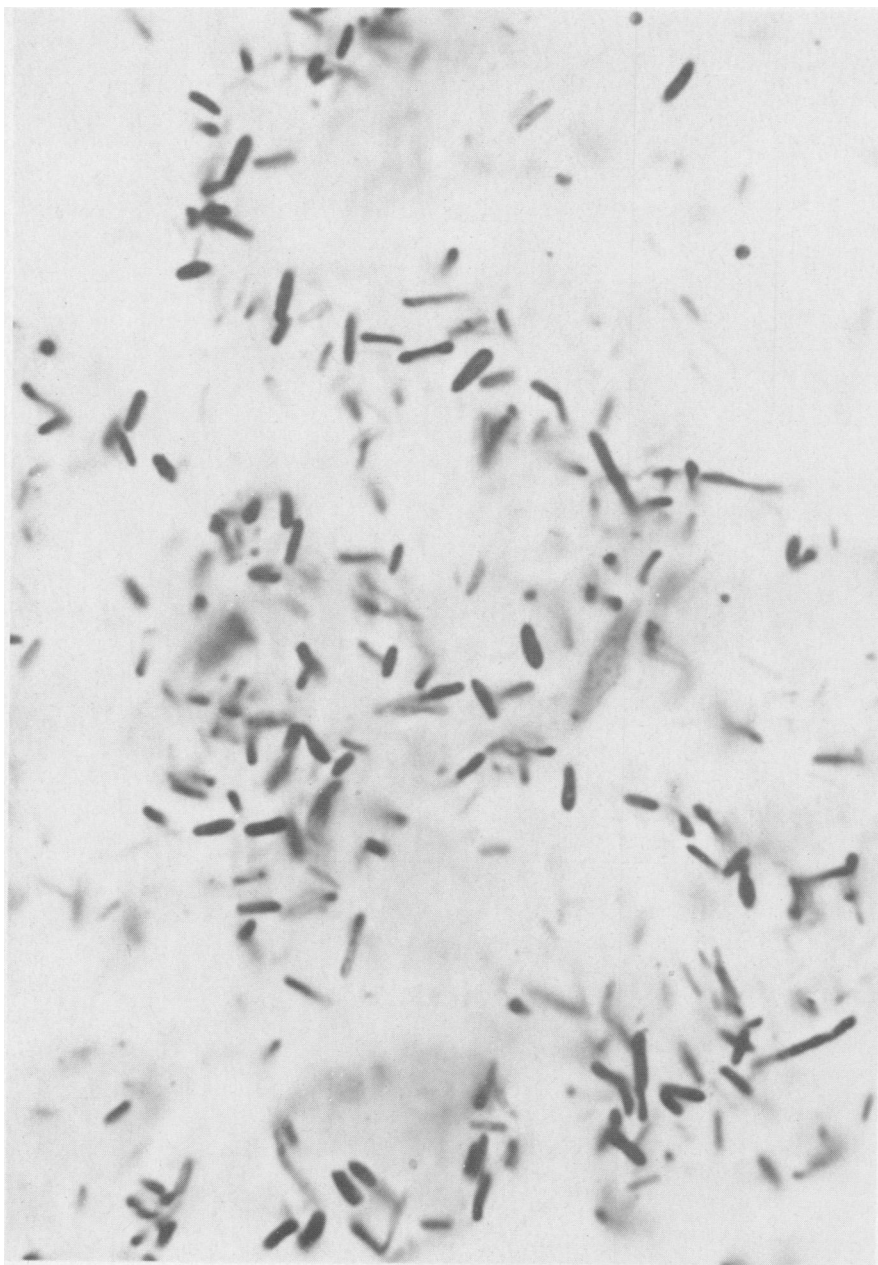


FIG. 1. Gram stain preparation of aspirated thigh fluid, $\times 1400$, showing large gram positive rods; cultures grew *Clostridium septicum*.

leukemia in remission, came to the emergency room with fatigue and myalgia of four days' duration. His temperature was 38.5 C, his pulse was 160 and respiratory rate was 45. Examination showed diffuse abdominal and bilateral thigh tenderness as well as scrotal and left thigh ecchymosis. The patient's white blood cell count was 35,200, 85% of which were blastocytes; his creatine phosphokinase level was 4700 mIU/ml, lactate dehydrogenase 1267 U/ml. Two hours after admission the patient became hypotensive and unresponsive, and he could not be resuscitated. Autopsy examination demonstrated gas gangrene of both thighs, right axilla, right shoulder; extensive crepitation of soft tissues and viscera; pyelonephritis with multiple abscesses; and acute myeloblastic leukemia with involvement of liver, spleen, lungs, kidneys, and small intestine. Blood culture specimens grew *C. septicum*.

Case 3.* A 53-year-old man, with diet-controlled diabetes, came

* Previously reported *New England Journal of Medicine* case report.⁵

to the emergency room with a 12-hour history of left shoulder pain and arm weakness. His temperature was 38.1 C, pulse was 140, and respirations were 48. Examination showed massive left shoulder edema, crepitation, and purple skin discoloration. Fluid aspiration specimens from bullous skin lesions demonstrated many gram positive rods. The patient's white blood cell count was 11,000 with 25% mature and 53% immature neutrophils; and his creatine phosphokinase level was 3020 mIU/ml. Radiographs of the patient's chest confirmed the presence of soft tissue gas. He quickly became hypotensive and apneic and was resuscitated. Antibiotic therapy was initiated, and three and one-half hours after admission to the hospital, the patient underwent forequarter left arm amputation. Extensive debridement of necrotic muscle extended across left chest, back, neck, and upper abdomen; internal oblique and intercostal muscles were found necrotic. The patient remained hypotensive, however, and died four hours later. Autopsy examination demonstrated extensive left arm myonecrosis; pulmonary edema; and a previously unsuspected 7 \times 6 \times 2 cm sigmoid colon

adenocarcinoma extending through serosa, metastatic to mesenteric lymph nodes. Wound and blood culture specimens grew *C. septicum*.

Case 4. A 69-year-old woman, with a history of diverticulitis, was admitted to the hospital with abdominal pain and weight loss. A radiograph obtained following sigmoidoscopy and biopsy of a colon mass demonstrated free intraperitoneal air, and the patient underwent exploratory laparotomy. A low anterior resection with end-sigmoid colostomy and Hartman turn-in procedure were performed for what proved to be a moderately differentiated adenocarcinoma extending into fat; the lymph nodes were free of tumor. A peritoneal fluid aspiration specimen grew *Bacteroides sp.*, and though afebrile the patient was administered penicillin and chloramphenicol for ten days after operation. On the sixteenth day after operation, the patient experienced a shaking chill, and her temperature was 39.8 C. The patient's white blood count was 26,900, with 74% mature and 19% immature neutrophils; blood cultures were obtained. Despite antibiotic therapy, the patient remained febrile and on the nineteenth day after operation she became hypotensive and died. No autopsy was performed. Blood culture specimens grew *C. septicum*.

Case 5. A 62-year-old man, with a past history of penicillin allergy and diabetes mellitus, developed abdominal wall myonecrosis two days following right colectomy and liver biopsy for metastatic colon adenocarcinoma. At surgical re-exploration, the colon anastomosis was intact and no abscess was seen. Antibiotic therapy was initiated, and the patient was transferred to the Massachusetts General Hospital. The patient's temperature on admission to the hospital was 40 C, and his pulse was 120. Crepitance, bullae, and erythema encompassed the right abdomen from axilla to thigh, including penis and scrotum. The patient's white blood cell count was 4,400, with 17% mature and 66% immature neutrophils. He underwent wide debridement of abdominal wall, chest wall, perineum, and thigh. Three days later Marlex® mesh was placed after further excision, and the following week meshed autograft skin was applied. Despite local infection control the patient developed respiratory, renal, and cardiac failure and died three weeks after admission to the hospital. Autopsy examination demonstrated severe coronary artery disease and colon adenocarcinoma metastatic to liver. Initial wound cultures had grown *C. septicum*.

Case 6. A 71-year-old man was admitted to the hospital with a two-day history of left foot numbness, swelling, and discoloration. In 1976, he had been treated with radiation and chemotherapy for unresectable rectal carcinoma metastatic to liver; pulmonary metastases in 1978 were treated with bilateral lung radiation. On admission to the hospital his temperature was 39 C, and his left leg was cold, swollen, and crepitant to the knee. The patient's white blood cell count was 7,900, with 53% mature and 33% immature neutrophils. He was administered antibiotics, and a guillotine above-knee amputation performed. One week later, the patient underwent revision and closure of his thigh stump and was discharged ten days following this. Four preoperative blood culture specimens grew *C. septicum*; 12 postoperative culture specimens were negative.

Case 7. A 53-year-old woman, who had had a right radical mastectomy for infiltrating duct carcinoma in 1962, underwent removal of a gangrenous appendix. One day later she developed a fever of 39 C, hypotension, and abdominal wall discoloration. Antibiotic therapy was initiated and the patient was transferred to the Massachusetts General Hospital. On examination the patient had extensive cellulitis of right abdomen, from the costal margin to the thigh. Her white blood cell count was 10,300, with 72% mature and 11% immature neutrophils. The patient's abdominal wall was widely debrided to the peritoneum, and dressed. On the eighth day after operation, the patient experienced evisceration and Marlex mesh was used to repair the abdominal wall defect. Granulations formed and, two weeks later, split thickness skin autografts were applied. Minimal additional debridement was required, and the patient was

discharged from the hospital on her eightieth hospital day. She has continued to do well and has no evidence of recurrent breast carcinoma. Culture specimens from aspirated right thigh fluid and the abdominal wound grew *C. septicum*.

Discussion

Each of our seven patients with *C. septicum* gangrene or sepsis also had malignant disease: four patients had colon carcinoma, two had leukemia, and one patient had breast carcinoma (Table 1). Most of these malignancies had been known and treated, but two were occult—leukemia discovered upon routine blood cell count in the emergency room (Patient 1), and metastatic sigmoid adenocarcinoma found at autopsy examination (Patient 3). One patient, by all indications, had been cured of her breast carcinoma, and that carcinoma cannot be implicated in the later myonecrosis. In six of the seven patients, however, the neoplasm was in an advanced state. Our series, thus, adds to the mounting evidence favoring the association of *C. septicum* infection and malignancy, and suggests that, in the patient with *C. septicum* infection, malignancy should be sought.

The nature of this relationship, though, remains unexplained. It seems likely that immunosuppression plays a role, perhaps a discrete form of immunosuppression common to patients with hematologic or colon malignancy but not, for example, to transplant patients or those with lung carcinoma. Debilitation may also place the cancer patient at added risk but, while three of our patients had undergone antecedent bowel operation, only one (Patient 4) was clinically debilitated. In short, it appears that *C. septicum* selectively infects this group of patients, suggesting it is an opportunistic organism requiring an unusual milieu, common to individuals with blood or bowel malignancy. This organism should be considered in the septic patient with known malignancy.

A final common factor is compromised intestinal wall, particularly in cecum or distal ileum, frequently on the basis of leukemic infiltration, bowel carcinoma, ischemia, or perforation. In Koransky's² series, 22 of 28 patients who underwent autopsy examination had a bowel portal of entry, 17 in distal ileum or cecum, and the other six had no entry site discovered. Ulcerative lesions of the bowel, often carcinoma, were present in seven of ten patients with nontraumatic myonecrosis, reported by Jendrzejewski et al.,⁴ and a bowel entry site may be postulated in five of our seven patients (Patients 1,3,4,5, and 7). Most investigators have proposed that the clostridial organism, residing in these areas of most suitable pH and osmolarity, is allowed access to extraluminal tissue or bloodstream and, in the patient at risk, proliferates.

TABLE 1. Clinical Summary of Patients with *C. septicum* Gangrene or Sepsis

Patient	Clinical State	Operation	Anti-biotic*	Isolate	Associated Condition†	Outcome
1. 50 years Male	Thigh gangrene abdominal pain	None	V, G, Ch	Thigh aspirate	Acute myeloblastic leukemia	Died
2. 29 years Male	Thigh and shoulder gangrene	None	None	Blood	Acute myeloblastic leukemia	Died
3. 53 years Male	Shoulder gangrene	Left arm forequarter amputation	P	Wound, blood	Metastatic adenocarcinoma sigmoid colon; AODM	Died
4. 69 years Female	Septicemia after low anterior resection	None	P, Ch	Blood	Duke's C adenocarcinoma sigmoid colon	Died
5. 62 years Male	Abdominal wall myonecrosis after right colectomy	Explor. laparotomy; debridement ×3; Marlex mesh repair	Ch, G, E	Wound	Metastatic colon adenocarcinoma; AODM	Died
6. 71 years Male	Leg gangrene	Guillotine above-knee amputation; stump closure	P, Cl, G	Blood	Metastatic adenocarcinoma of rectum	Alive
7. 53 years Female	Abdominal wall myonecrosis after appendectomy	Debridement; Marlex mesh repair	P, Cl, G	Wound	Infiltrating duct carcinoma of breast	Alive

* Ch: chloramphenicol; Cl: clindamycin; E: erythromycin; G: gentamicin; P: penicillin; V: vancomycin.

† AODM: adult-onset diabetes mellitus.

Thus, though mechanisms remain unclear, the relationships themselves—*Clostridium septicum*, malignancy, bowel portal of entry—have been established, and surgeons in particular must be aware of them. They are often called first to see the patient with gangrene or compromised bowel, and only through a high index of suspicion and prompt treatment can the present 50–70% mortality rate be improved. Of Alpern and Dowell's¹ 27 patients, for example, 13 of 15 treated with antibiotics (nine with penicillin; the others with cephalothin, chloramphenicol, colistin) survived while 11 of 12 untreated patients died; surgical treatment is not discussed in their report. In a later series² 18 of 40 patients who received antibiotics (penicillin, cephalothin, chloramphenicol, or carbenicillin) within 12 hours of the onset of infection survived. Treatment failures were felt to have lacked necessary surgery or adequate blood levels of antibiotics. The results of the present small series show that, despite prompt use of appropriate antibiotics in all but one patient, the only survivors were two of the four patients who underwent extensive operative debridement. Until further surgical experience with *C. septicum* suggests specific management, we feel that treatment should follow surgical principles established for any form of gas gangrene, i.e., aggressive operative debridement of all involved or devitalized tissues.⁶

In summary, we feel the following merit emphasis: 1) In a patient with isolates of *C. septicum*, malignancy (e.g., hematologic or intestinal) should be sought.

2) As a corollary, in the septic patient with known malignancy, particularly hematologic or bowel malignancy, anaerobic as well as aerobic cultures should be obtained. If the causative organism is in doubt, antibiotics appropriate for anaerobic infection (penicillin, chloramphenicol, carbenicillin, clindamycin) should be administered. Penicillin remains the drug of choice for *C. septicum*. 3) In a patient with evidence of clostridial myonecrosis or sepsis and no external source, the cecum or distal ileum should be considered a likely site. 4) Only the institution of aggressive medical and surgical treatment will save these patients.

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